UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: May 10, 2016

SUBJECT: **ADBAC:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of January 21st: Recommendation on the Requirements for Neurotoxicity (Acute and Subchronic) Studies, Subchronic Inhalation Study and Immunotoxicity study.

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TO: LT Jonathan Leshin
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MEETING ATTENDEES

HASPOC Members: Elizabeth Mendez, Jeff Dawson, John Kough, Jonathan Chen, Jonathan Leshin, Kelly Lowe, Michael Metzger, Ray Kent, Sarah Gallagher, Uma Habiba

Presenters: Jonathan Leshin, Tim Dole

Other Attendees: Anwar Dunbar, Donna Judkins, Jaime D'Agostino, Matt Lloyd, Nancy McCarroll, Sarah Dobreniecki, Seiichi Muraski, Tim McMahon, William Donovan

I. PURPOSE OF MEETING

The Risk Assessment and Science Support Branch of the Antimicrobials Division is currently preparing preliminary workplan for registration review in support of alkyl dimethyl benzyl ammonium chloride (ADBAC) group II quaternary ammonium compounds. The toxicology database for ADBAC is complete except for the neurotoxicity (acute and subchronic) studies, the subchronic inhalation toxicity study and the immunotoxicity study that are required in accordance with the current 40 CFR Part 158W Toxicology Data Requirements. The Hazard and Science Policy Council (HASPOC) met on January 21st to discuss the need for these studies to support registration review.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

ADBAC is a non-halogenated benzyl substituted group II quaternary ammonium compound. The ADBAC chemical case is comprised of more than 20 compounds that are structurally similar quaternary ammonium compounds (i.e., referred to as "quats") that are characterized by having a positively charged nitrogen covalently bonded to three alkyl group substituents and a benzyl substituent. In finished form, these quats are salts with the positively charged nitrogen (cation) balanced by a negatively charged molecule (anion). The most common anion for the quats in this cluster is chloride. However, other anions, such as saccharine and bromide are also used. Chemicals in this group are used as algicides, bacteriocides, bacteriosats, wood preservatives, fungicides, fungistats, virucides, tuberculocides, insecticides, microbicides, microbiostats, molluscides, deodorants, disinfectants and sanitizers. There are also food uses of this chemical. ADBAC formulations are added directly to water in swimming pools, decorative ponds/fountains, spas, cooling water towers, oil field drilling muds and packing fluids, small process water systems, humidifiers, and in applications related to cut flowerss. ADBAC formulations are diluted in water to treat hard nonporous surfaces in institutional, commercial, industrial, and residential settings by fogging, immersion, wiping, mopping, aerosol/trigger spray, and low pressure and high-pressure spray. Some impregnated wipes are dampened with water prior to use while others are pre-moistened. For the treatment of wood, ADBAC is applied by a blender/spray system, diptank, spray box, or pressure treatment.

Pursuant to PR Notice 88-2, grouping of quaternary ammonium compounds was allowed, based on the numerous chemical structures that represent these types of chemicals. Grouping was allowed into 4 broad categories, based on chemical structure: Group I quaternary ammonium compounds (alkyl or hydroxy alkyl substituted compounds); Group II non-halogenated benzyl

substituted quaternary ammonium compounds (ADBAC as representative); Group III di- and trichlorobenzyl substituted quaternary ammonium compounds; and Group IV, quaternary ammonium compounds with unusual substituents. ADBAC, or alkyl dimethyl benzyl ammonium chloride, is, as stated above, a member of the Group II class of quaternary ammonium compounds. Hazard data generated for ADBAC is representative of the hazard associated with this class of quaternary ammonium chemicals.

ADBAC is toxic via the oral, dermal and inhalation route (Toxicity Category II). Due to corrosivity, the eye irritation test was waived and given Toxicity Category I. ADBAC was an extreme dermal irritant (Toxicity Category I) but not a dermal sensitizer or a photosensitizer.

In a subchronic oral toxicity study in rats, ADBAC was found to have mainly generalized irritation effects (decreased body weight gain, food consumption), and occurred at relatively high doses (LOAEL of 31 mg/kg/day in males, 77 mg/kg/day in females). This result was also observed in chronic toxicity studies in rats and mice, where effects were also general in nature (decreased body weight gain and food consumption), and occurred at relatively high doses. In a 21-day dermal toxicity study in guinea pigs, no significant systemic effects were observed using a chemical mixture of 4% ADBAC/6% DDAC, but denuding of the epidermal layer was observed at the highest dose tested, 1000 mg/kg/day. In a 90-day dermal toxicity study in rats, dermal applications of ADBAC to rats did not elicit systemic or dermal toxicity up to the highest dose tested, 20 mg/kg/day, before dermal irritation became significant. There are no inhalation studies in the database and inhalation currently uses a maternal developmental endpoint in rabbits for the POD.

ADBAC has been examined for effects on development of the mammalian fetus and effects on reproductive function. In developmental studies with rats and rabbits, developing fetuses showed no increased sensitivity to the toxicity of ADBAC in relation to adult animals. In a 2-generation reproductive toxicity study, effects on rat pups were observed in the absence of maternal toxicity, raising some concern for the effects of ADBAC on reproductive function. However, the effects observed were non-specific (decreased pup body weight and weight gain during lactation), and there were no effects of ADBAC on reproductive indices.

In a chronic toxicity study in dogs, systemic toxicity was observed at 13.1 mg/kg/day in males and 14.6 mg/kg/day in females as reduced body weight gain (approximately 10% reduction) after 52 weeks of exposure. Food consumption was decreased in the high dose males and females for the entire study period (approximately 15% reduction in males and 5% reduction in females). Based on the data in this study, the systemic toxicity NOAEL was 120 ppm (3.79 mg/kg/day in males, 3.67 mg/kg/day in females) and the LOAEL was 400 ppm (13.1 mg/kg/day in males, 14.6 mg/kg/day in females) based on reduced body weight gain.

ADBAC has been tested for carcinogenicity in long term studies with both rats and mice. In both studies, tested to adequate dose levels, ADBAC was negative for induction of tumors in both species. This result is supported by results of testing in a battery of mutagenicity studies, including an HGPRT/CHO forward mutation assay, an in vivo bone marrow chromosome aberration assay, and an unscheduled DNA synthesis (UDS) assay, which show ADBAC to be negative for mutagenic effects.

III. STUDY WAIVER REQUEST

a. Subchronic Inhalation Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including: (1) its degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. ADBAC has a vapor pressure of at 3.53 $x10^{-12}$ mm Hg at 25 °C and the Henry's Law Constant is 5.03 x 10^{-7} Pa m^3 mol^{-1} @ 20°C. However, low vapor pressure and/or Henry's law constant does not preclude exposure to aerosolized droplets or particles/dusts.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. ADBAC is applied with fogging, immersion, wiping, mopping, aerosol/trigger spray, and low pressure and high-pressure spray along with blender spray, diptank and other aerosol generating methods.

3. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than of the LOC as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here.

   The LOC for all durations is currently 1000 (10X inter-species, 10X intra-species, 10X route to route extrapolation). All MOEs are calculated using the oral data from the rabbit developmental study. MOEs for occupational use of ADBAC range from a low of 6 for small process water systems liquid pour to a high of 390,000,000 for

mixing/loading/applying liquid concentrates with a handgun sprayer on ornamental shrubs and seedlings in a field. Some other uses below the LOC include mixing loading agricultural fogging (26), medical premises (95), wood preservation non pressure treatment (84) and wood preservation airless sprayer (17), hard surfaces wiping (590) and low pressure hand wand (380) in an agricultural setting, food handling hard surfaces wiping (580) and commercial/institutional premises hard surface wiping (360). The MOEs for residential use range from 820 for wiping on indoor hard surfaces to 38,000 for use in air deodorizers. While exposure to humidifiers have a theoretical MOE below the LOC, data from ORD indicate that there is no release of ADBAC. Generally for spray type disinfectants, respirators would not be used for mitigation due to the use pattern or site of use (e.g., like hospitals).

4. **Evidence for inhalation toxicity in the database of other similar chemicals:** ADBAC is the representative member for the group II quaternary ammonium compounds and there is no data from other members of this group available. A registrant working group proposed to use a 28-day inhalation study from DDAC, which is the representative member of the group I quaternary ammonium compounds. This study set a LOAEC of 0.08 mg/m^3 and no NOAEC.. The registrant working group states that due to similarity of effect (irritation/corrosion), similarity in structure and antimicrobial mechanism of action that the study for Group I Quats (DDAC) should be sufficient for Group II Quats (ADBAC). These compounds both share the same reactive center (a positively charged quaternary nitrogen atom) with different side chains.

   The HASPOC agreed that the two compounds cause similar effects (irritation/corrosion). While the chemical groups are distinct based on their side chains, for point of contact toxicity following inhalation exposure, which does not involve absorption, distribution or metabolism, the similarity of reactive groups are likely to be the driver in the toxic effects. Since the reactive groups are the same for both ADBAC and DDAC (reactive quaternary ammonium groups) the toxicity is likely to be similar. Based on the data available, it appears that DDAC may be more irritating than ADBAC; the maternal NOAEL for the DDAC rat developmental study is 1 mg/kg/day whereas the maternal NOAEL for the ADBAC rat developmental study is 10 mg/kg/day. Taken together, an inhalation study with ADBAC is not likely to result in different effects or a lower point of departure than the current DDAC inhalation study.

While the use of oral data resulted in MOEs below the LOC which indicates that route specific data is needed, the HASPOC recommends, based on a WOE approach and considering all available hazard and toxicity data that the subchronic inhalation toxicity study **is not required** for ADBAC and the 28 day inhalation study from DDAC can be bridged across to fulfill this data gap. This approach considered all of the available hazard and exposure information for ADBAC including: 1) the DDAC inhalation study is likely to be protective given that DDAC is equally or slightly more toxic when comparing the existing oral datasets for the chemicals, 2) both share sufficient similarity as quaternary ammonium compounds given the nature of the point of contact toxicity and 3) given the corrosive irritant nature of the chemicals, it is appropriate to bridge between them.

b. Neurotoxicity Studies

Acute neurotoxicity (ACN) and subchronic neurotoxicity (SCN) studies are required in the 2007 revised 40 CFR Part 158 Toxicology Data Requirements because they provide important scientific information on potential nervous system effects from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory, and histopathology of the nervous system.

With respect to considering whether the ACN and SCN studies should be required for ADBAC, the HASPOC used the following WOE approach:

1. **Evidence for potential neurotoxicity in the ADBAC database of toxicology studies:** There was no evidence of neurotoxicity from ADBAC exposure in the toxicological database. No clinical signs indicating neurotoxicity were observed in the subchronic oral toxicity study in rats, the chronic toxicity/carcinogenicity study in rats, the 2-generation reproduction study in rats, the carcinogenicity study in mice, 90 day dermal toxicity study in rat or the 21-day dermal toxicity study in guinea pigs. While there were clinical signs present in the developmental studies (ataxia, prostration, hypoactivity), these were not considered related to neurotoxicity, and instead they were considered secondary to the irritation effects.

2. **Evidence for neurotoxicity in the database of other similar chemicals:** There are no related chemicals. ADBAC is the representative chemical for all group II quaternary ammonium compounds and no data from other members of the group are available.

3. **Risk assessment considerations:** The available data indicate that neurotoxicity is of low concern for ADBAC and would not provide a lower POD for the risk assessment. All existing data indicates irritation as the mechanism of toxicity for Group II quaternary ammonium compounds. No acute dietary endpoint was selected for ADBAC because of the anticipated low acute exposure (0.1% concentration) via indirect food exposure and there are no direct food uses.

HASPOC recommends, based on a WOE approach, that the neurotoxicity studies (ACN and SCN) **not be required for** ADBAC. This approach considered all of the available hazard and exposure information for ADBAC including: 1) no evidence of neurotoxicity in the toxicity database for ADBAC; 2) the presence of clinical signs in the developmental study are not considered neurotoxic but instead secondary to irritation, 3) the low acute exposure (0.1% concentration) via indirect food exposure with no direct food use indicates that an acute dietary endpoint is unlikely to be selected and 4) neurotoxicity studies are not likely to identify a lower POD or a more sensitive endpoint for the risk assessment of ADBAC.

c. Immunotoxicity

Evidence for potential immunotoxicity in the ADBAC database of toxicology studies: ADBAC has no indications of immunotoxicity in the database.

Table 1. Summary of ADBAC Immunotoxicity Potential in Toxicology Studies.	
Parameter	**Findings**
Hematology Indicators (WBC changes)	None
Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	None
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	None
Toxicity Profile (Target Organs)	None

Evidence for potential immunotoxicity from the database of toxicology studies for other pesticides or structure activity relationship (SAR) chemicals -retrospective analysis: There are no related chemicals. ADBAC is the representative chemical for all group II quaternary ammonium compounds and no data from other members of the group are available.

Based on a WOE approach, considering all of the available hazard and exposure information, the HASPOC recommends that the immunotoxicity study **be waived** at this time for ADBAC based the lack of indications of immunotoxicity in the existing toxicity database.

IV. HASPOC RECOMMENDATIONS

The HASPOC has concluded, based on a WOE approach and considering all of the available ADBAC hazard and exposure data that the neurotoxicity (ACN and SCN) studies and immunotoxicity study **are not required**. The subchronic inhalation study **is not required** due to bridging with the DDAC 28-day inhalation study.